

We Claim:

- 1 1. A method of generating a genetic reference dataset for use in the
2 determination of the predicted probability for an individual of having a susceptibility
3 for a developmental disorder due to genetic factors or for developing a developmental
4 disorder due to genetic factors or for having offspring that develop a developmental
5 disorder due to genetic factors comprising:
6 (a) collecting a biological sample from a human subject; wherein the
7 human subject is selected from the group consisting of a diagnostic proband, a blood
8 relative of the diagnostic proband, an affected proband, a blood relative of the
9 affected proband, a control proband, and a blood relative of the control proband;
10 wherein the biological sample contains nucleic acids and/or proteins from the human
11 subject;
12 (b) analyzing the nucleic acids and/or proteins from the biological sample;
13 wherein said analyzing results in a partial or full genotype for the alleles of the genes
14 involved in folate, pyridoxine, and/or cobalamin metabolism; wherein said partial or
15 full genotype forms a dataset of genetic explanatory variables for the human subject;
16 and
17 (c) compiling the dataset of genetic explanatory variables from multiple
18 human subjects into a genetic reference dataset.
- 1 2. A method of generating a genetic and environmental reference dataset for use
2 in the determination of the predicted probability for an individual of having a
3 susceptibility for a developmental disorder due to genetic factors and environmental
4 factors or for developing a developmental disorder due to genetic factors and
5 environmental factors or for having offspring that develop a developmental disorder
6 due to genetic factors and environmental factors comprising:
7 (a) obtaining dietary and epidemiological information for environmental
8 explanatory variables for the human subjects of Claim 1; and

3. The method of Claim 2 wherein the developmental disorder is selected from the group consisting of schizophrenia, spina bifida cystica, Tourette's syndrome, dyslexia, conduct disorder, attention-deficit hyperactivity disorder, bipolar illness, autism, chronic multiple tic syndrome and obsessive-compulsive disorder.

(a) obtaining dietary and epidemiological information for environmental explanatory variables for a human subject; wherein the human subject is selected from the group consisting of a diagnostic proband, a blood relative of the diagnostic proband, an affected proband, a blood relative of the affected proband, a control proband, and a blood relative of the control proband; and

1 5. A method of estimating the genetic susceptibility of an individual to have or
2 to develop a developmental disorder comprising:

(a) collecting a biological sample from one or more participants; wherein a participant is either the individual or a blood relative of the individual; and wherein the biological sample contains nucleic acids and/or proteins of the participant;

6 (b) analyzing the nucleic acids and/or proteins from the biological sample;
7 wherein said analyzing results in a partial or full genotype for the alleles of the genes

1 6. The method of Claim 5 wherein said analyzing the combined genetic dataset
2 is performed by binary linear regression.

1 8. The method of Claim 7 further comprising the step of :
2 (g) testing the model for goodness of fit.

1 9. The method of Claim 8 wherein the binary linear regression is performed with
2 the SAS system.

1 10. The method of Claim 5 wherein the developmental disorder is selected from
2 the group consisting of schizophrenia, spina bifida cystica, Tourette's syndrome,
3 dyslexia, conduct disorder, attention-deficit hyperactivity disorder, bipolar illness,
4 autism, chronic multiple tic syndrome and obsessive-compulsive disorder.

1 11. The method of Claim 10 wherein the developmental disorder is schizophrenia
2 and the individual is suspected of being genetically susceptible of having or for
3 developing schizophrenia.

1 12. The method of Claim 11 wherein the individual is suspected of being
2 genetically susceptible for having or for developing schizophrenia because a blood
3 relative has schizophrenia.

1 13. The method of Claim 12 wherein the blood relative is a parent, a sibling, or a
2 grandparent.

1 14. The method of Claim 13 wherein the blood relative is a parent and wherein the
2 parent is the mother of the individual.

1 15. A method of estimating the genetic and environmental susceptibility of an
2 individual to have or to develop a developmental disorder comprising:

3 (a) collecting a biological sample from one or more participants; wherein
4 a participant is either the individual or a blood relative of the individual; and wherein
5 the biological sample contains nucleic acids and/or proteins of the participant;

6 (b) analyzing the nucleic acids and/or proteins from the biological sample;
7 wherein said analyzing results in a partial or full genotype for the alleles of the genes
8 involved in folate, pyridoxine, and/or cobalamin metabolism; and wherein said partial
9 or full genotype forms a dataset of genetic explanatory variables for the participants;

10 (c) obtaining dietary and epidemiological information for environmental
11 explanatory variables for the participants; wherein said information forms a dataset of
12 environmental explanatory variables for the participants;

13 (d) adding the datasets of genetic explanatory variables obtained from
14 steps (a) and (b) and the dataset of environmental explanatory variables of step (c) to
15 a genetic and environmental reference dataset therein forming a combined genetic and
16 environmental dataset;

17 (e) formulating a model comprising the genetic and environmental
18 explanatory variables obtained from the participants; and

19 (f) analyzing the combined genetic and environmental dataset by binary
20 logistic regression;

21 wherein a predicted probability for the individual of having or developing a
22 developmental disorder is determined; and wherein the genetic and environmental
23 susceptibility of an individual to have or to develop a developmental disorder is
24 estimated.

1 16. The method of Claim 15 further comprising the step of :

2 (g) modifying the model by adding or subtracting a genetic or
3 environmental explanatory variable; and re-analyzing the combined genetic and
4 environmental dataset by binary logistic regression; wherein a model is chosen that
5 best fits the data.

1 17. The method of Claim 16 further comprising the step of :

2 (h) testing the model for goodness of fit.

1 18. The method of Claim 17 wherein the binary linear regression is performed
2 with the SAS system.

1 19. A method of estimating the susceptibility of an individual to have offspring
2 that develop a developmental disorder comprising:

3 (a) collecting a biological sample from one or more participants; wherein
4 a participant is either the individual or a blood relative of the individual; and wherein
5 the biological sample contains nucleic acids and/or proteins of the participant;

6 (b) analyzing the nucleic acids and/or proteins from the biological sample;
7 wherein said analyzing results in a partial or full genotype for the alleles of the genes
8 involved in folate, pyridoxine, and/or cobalamin metabolism; and wherein said partial
9 or full genotype forms a dataset of genetic explanatory variables for the participants;

10 (c) adding the datasets of genetic explanatory variables obtained from
11 steps (a) and (b) to a genetic reference dataset therein forming a combined genetic
12 dataset;

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- 13 (d) formulating a model comprising the genetic explanatory variables
 14 obtained from the participants; and
 15 (e) analyzing the combined genetic dataset by binary logistic regression;
 16 wherein a predicted probability for the individual to have offspring that
 17 develop a developmental disorder is determined; and wherein the genetic and
 18 environmental susceptibility of an individual to have offspring that develop a
 19 developmental disorder is estimated.

1 20. The method of Claim 19 further comprising the step of :

- 2 (f) modifying the model by adding or subtracting a genetic explanatory
 3 variable; and re-analyzing the combined genetic dataset by binary logistic regression;
 4 wherein a model is chosen that best fits the data.

1 21. The method of Claim 20 further comprising the step of :

- 2 (g) testing the model for goodness of fit.

1 22. The method of Claim 21 wherein the binary linear regression is performed
 2 with the SAS system.

1 23. The method of Claim 22 wherein the individual is a pregnant woman.

1 24. A method of lowering the risk of a pregnant woman who has been determined
 2 by the method of Claim 23 to be susceptible to have offspring that develop a
 3 developmental disorder comprising administering methylfolate, cobalamin or
 4 pyridoxine to the pregnant woman, wherein said administering lowers the risk of the
 5 pregnant woman of giving birth to offspring with a developmental disorder.

1 25. A method of determining if any treatment is advisable for a pregnant woman
 2 who has been determined by the method of Claim 23 to be susceptible to having
 3 offspring that develop a developmental disorder comprising determining the

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1 33. A PCR primer that can be used to distinguish SEQ ID NO:42 from the
2 nucleotide sequence selected from the group consisting of SEQ ID NO:41 and SEQ
3 ID NO:45.

1 34. The PCR primer of Claim 33 that comprises 10 to 50 consecutive nucleotides
2 from the nucleotide sequence selected from the group of SEQ ID NO: 41, the
3 complementary strand of SEQ ID NO: 41, SEQ ID NO:42, the complementary strand
4 of SEQ ID NO: 42, SEQ ID NO:45, and the complementary strand of SEQ ID NO:
5 45.

1 35. The PCR primer of Claim 34 wherein the 10 to 50 consecutive nucleotides are
2 from nucleotides 350 to 530 of SEQ ID NO:41.

1 36. The PCR primer of Claim 35 having the nucleotide sequence of 5'-CTA AAC
2 TGC ATC GTC GCT GTG-3' (SEQ ID NO:38).

1 37. The PCR primer of Claim 36 wherein the 10 to 50 consecutive nucleotides are
2 from the complementary strand of nucleotides 550 to 850 of SEQ ID NO:41.

1 38. The PCR primer of Claim 37 having the nucleotide sequence of 5'-AAA AGG
2 GGA ATC CAG TCG G-3' (SEQ ID NO:39).

1 39. An isolated nucleic acid that hybridizes under standard hybridization
2 conditions to a nucleic acid having the nucleotide sequence
3 ACCTGGGCGGGACGCGCCA (SEQ ID NO:40) or a sequence complementary to
4 SEQ ID NO:40; wherein said isolated nucleic acid consists of 12 to 48 nucleotides.

1 40. An isolated nucleic acid that hybridizes to the nucleotide sequence of SEQ ID
2 NO:42, but not to the nucleotide sequence of SEQ ID NO:41; when said hybridizing
3 is performed under identical conditions.

1 46. The method of Claim 1 wherein said analyzing the nucleic acids and/or
2 proteins from the biological sample comprises determining if the biological sample
3 contains the genetic variant of human dihydrofolate reductase having a nucleotide
4 sequence with a 19 base-pair deletion spanning nucleotides 540 to 558 of the
5 nucleotide sequence of SEQ ID NO:41; and wherein the genetic variant of human
6 dihydrofolate reductase is an explanatory variable.

- 1 47. The method of Claim 46 wherein said determining is performed by a method
2 selected from the group consisting of PCR, special PCR, RT PCR, RFLP analysis,
3 SSCP, and FISH.